ALPRAZOLAM EXTENDED-RELEASE- alprazolam tablet, extended release
Bryant Ranch Prepack

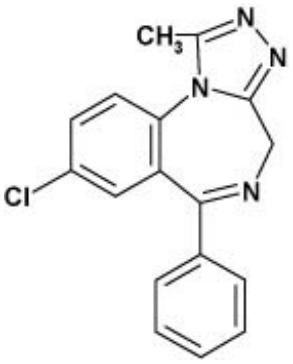
Alprazolam Extended-Release Tablets CIV 0.5 mg, 1 mg, 2 mg and 3 mg Rx only

DESCRIPTION

Alprazolam extended-release tablets contain alprazolam, USP which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4 -triazolo [4,3-α] [1,4] benzodiazepine. The molecular formula is C H ClN which corresponds to a molecular weight of 308.76. *H-s*$_{17134}$

The structural formula is:



C IV

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each alprazolam extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam, USP. The inactive ingredients are colloidal silicon dioxide, hypromellose, lactose monohydrate, and magnesium stearate. In addition, the 1 mg and 3 mg tablets contain D & C yellow No. 10 and the 2 mg and 3 mg tablets contain FD&C blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

INDICATIONS AND USAGE

Alprazolam extended-release tablets are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with alprazolam extended-release tablets conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see). **CLINICAL STUDIES**

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of alprazolam extended-release tablets has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam extended-release tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam extended-release tablets may be used in patients with open angle glaucoma who are receiving appropriate therapy, but are contraindicated in patients with acute narrow angle glaucoma.

Alprazolam extended-release tablets are contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see and). **CLINICAL PHARMACOLOGY,WARNINGSPRECAUTIONS - Drug Interactions**

WARNINGS

Dependence and Withdrawal Reactions, Including Seizures

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see). Even after relatively short-term use at doses of ≤ 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day. **DRUG ABUSE AND DEPENDENCE**

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received alprazoalam

extended-release tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received alprazolam tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to alprazolam tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%-93% of patients treated with alprazolam tablets tapered completely off therapy compared to 89%-96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with alprazolam extended-release tablets. In two cases, the patients had completed 6 weeks of treatment with alprazolam extended-release tablets 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued alprazolam extended-release tablets, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with alprazolam extended-release tablets 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of alprazolam tablets, the immediate release form of alprazolam. Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24-72 hours after discontinuation (see for recommended tapering and discontinuation schedule). **DOSAGE AND ADMINISTRATION**

PRECAUTIONS

Information for Patients

To assure safe and effective use of alprazolam extended-release tablets, the physician should provide the patient with the following guidance.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.

5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.
7. Some patients may find it very difficult to discontinue treatment with alprazolam extended-release tablets due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

Laboratory Test

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

Drug Interactions

Drug/Laboratory Test Interactions

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic in the DNA Damage/Alkaline Elution Assay or the Ames Assay. *in vitro*

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy

Teratogenic Effects: Pregnancy Category D: (see section). **WARNINGS**

Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery

Alprazolam has no established use in labor or delivery.

Nursing Mothers

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

Pediatric Use

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

Geriatric Use

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see and). **CLINICAL PHARMACOLOGYDOSAGE AND ADMINISTRATION**

ADVERSE REACTIONS

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with alprazolam extended-release tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

DRUG ABUSE AND DEPENDENCE

OVERDOSAGE

DOSAGE AND ADMINISTRATION

Alprazolam extended-release tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

Manufactured by: Corepharma LLC Middlesex, NJ 08846

Manufactured for: Rising Pharmaceuticals, Inc. Allendale, NJ 07401 February 2007 MF # 539-01

Alprazolam 0.5mg (CIV) Tablet

ALPRAZOLAM EXTENDED-RELEASE

alprazolam tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-1541(NDC:64980-140)
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	0.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE (White)	**Score**	no score
Shape	ROUND (round)	**Size**	10mm
Flavor		**Imprint Code**	cor;187
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-1541-1	15 in 1 BOTTLE		
2	NDC:63629-1541-2	30 in 1 BOTTLE		
3	NDC:63629-1541-3	20 in 1 BOTTLE		
4	NDC:63629-1541-4	100 in 1 BOTTLE		
5	NDC:63629-1541-5	90 in 1 BOTTLE		
6	NDC:63629-1541-6	60 in 1 BOTTLE		
7	NDC:63629-1541-7	120 in 1 BOTTLE		
8	NDC:63629-1541-8	28 in 1 BOTTLE		
9	NDC:63629-1541-9	2 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077996	03/28/2007	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-1541) , RELABEL(63629-1541)